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Since 1825

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# E D I T O R I A L

## **A SIGN OF PROGRESS**

**T**HE meeting of representatives of pharmacy and medicine held in Chicago in January is one of the most promising signs of better interprofessional relations that we have seen for a long time. This Committee included representatives of both of our national pharmaceutical associations and this, in itself, is heartening for, only too often, the A. Ph. A. and the N. A. R. D. have gone their separate ways in meeting a problem of concern to both.

While this first meeting was largely exploratory in nature, some solid accomplishment resulted. The representatives of the medical profession asked the representatives of pharmacy to prepare a statement for presentation to the American Medical Association's Judicial Council and Council on Constitution and By-Laws—such statement to have a bearing on a possible amendment of the principles of ethics of the A. M. A. with regard to the ownership of pharmacies by physicians. It was also suggested that representatives of pharmacy and medicine meet at regular intervals to discuss matters of mutual concern.

In reading the published statements coming from this top-level meeting of pharmacy and medicine, one cannot but agree with the statement of the pharmacy representatives that every effort should be made "to avoid any action which may have a tendency to aggravate rather than reduce tension between the two professions". In this we concur now that some means has been established at top-level whereby the voice and interests of pharmacy can be made known. We are not, however, of the opinion that nothing should have been said and no adverse comment made by the pharmaceutical press following the change in the Code of Ethics by the A. M. A. which caused all of this trouble in the first place. We are not at all sure that, had we swallowed our chagrin quietly, there would, today, be such a top-level joint committee giving attention to the problem.

As we look about us in all of the affairs in which humans participate—it does not seem to matter on what social, economic, or

political level we go—a group which takes repressive or discriminatory action against them calmly and quietly are apt to lose their collective “shirts”. If labor had permitted industry to exploit it without complaint, labor today would not have the position it now enjoys. If any minority group is afraid to insist on its rights, the persons comprising it will soon taste persecution and oppression. On the political scene, the colonial peoples of the world would never have independence if they accepted the domination of a colonial power without resistance.

Is there anyone so naïve to believe that pharmacy's rights and prerogatives never require vehement assertion and positive action when they are threatened? There is nothing about the physician which raises him above the human level in spite of his professional skill and integrity. Even the Church has had to fight at times to protect its interests and, unfortunately, the fight has not always been successful. Had the Church been less militant, would it have survived? We rather doubt it.

In conclusion then, we (at least, this editor) are not at all concerned that we reacted rather strongly when it appeared that pharmacy's sphere was open to invasion. We are, however, greatly pleased that a positive approach has now been taken. We hope, and have every reason to believe, that the difficulties which arose can be ironed out to everyone's satisfaction. Actually, in the final analysis, the unfortunate past incident may serve to promote better relations between the two professions.

L. F. TICE



## THE HORNS OF THE SCIENTIFIC DILEMMA \*

By Gustav J. Martin \*\*

**S**EMANTICS, the branch of linguistics dealing with the meaning of words, is a dangerous thing. If you follow the pattern of semantic investigation, you almost invariably must concede that all you have said has in fact no meaning. In some degree, I hope to avoid this unfortunate verbal circle. So I attempt to define what I mean by the title "The Horns of the Scientific Dilemma."

"Dilemma" is defined as a special type of reasoning which in its commonest form offers in conclusion two alternatives. These may be palatable or unpalatable. The expression "Horns of a Dilemma" has come to mean the equally undesirable alternatives between which a choice must be made. Actually, therefore, I should immediately change the title of this discussion because the alternatives to be considered are not undesirable and in fact no choice need be made. My excuse for retaining the title then must be that language is a living thing and subject to minor modifications in accordance with the stress of the situation. There is a degree of stress in any lecture and therefore semantics is over-ruled.

The horns of the scientific dilemma are those of analysis and integration. The evolution of science has been most intimately associated with analysis and this is the normal course of events. Analysis offers a picture of a practical, real world but it offers that picture in tiny fragments. It is a means to an end which has unfortunately been given the stature of the final goal. Our pattern of learning relates to feats of memory and most frequently those feats of memory have no significance in the pattern of the future. Before I went to medical school, I took a course in human anatomy at my undergraduate university; I repeated that same course while working for a graduate degree; and finally I most reluctantly returned to the battle of the scalpel and the dissecting scissors in medical school. Three times I passed from toe to scalp; three times I learned the origin, course and

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\* Delivered at the Founders' Day Convocation, Philadelphia College of Pharmacy and Science, February 23, 1956.

\*\* Vice-President and Director of Research, National Drug Co., Philadelphia, Pa.

distribution of the twelve cranial nerves; three times I reduced to memory the rime of *On Old Olympus Treeless Tops a Finn and German View Some Hops*. Today, I still have frequent indirect contact with the hops but the twelve cranial nerves originate, course about and distribute themselves with little help from me. The analysis essential to the determination of the textbook picture of the cranial nerves is a worthy, though somewhat boring project. But of what value is it to an endeavor to achieve some concept of science as a totality? It is my belief that it would have been much better to expose the student to the general idea of the existence of cranial nerves and perhaps let him view an anatomical demonstration thereof but not clutter up his brain with an infinity of analytical detail having no basic meaning.

Today, the vast majority of individuals in the field of science are devoting themselves to analysis. I would venture a guess that there are no more than two hundred persons in the United States who can be designated as integrative scientists. These are the neglected and forgotten men of science. Awards, accolades, recognition are heaped upon the analyst but the integrator is essentially ignored. Generally speaking, Nobel Prizes, the supreme modern recognition of the scientist, are awarded to analysts. Let me repeat, my plea is not against the analyst but against the abandonment of integration in deference to the easier path of analysis.

The design of modern society is one aimed at crushing creativity, at the elimination of the individual. This has a strange bitter merit. When I first read of the "societal organism", I felt strongly that the mind which created the concept was a strangely evil one. The idea of each and every human being as a kind of wild, primitive form being slowly integrated into a vast unit in a manner precisely parallel to that in which single cells were formed eventually into the complex human body was anything but appealing and yet this is precisely what is happening. A society has been designed to protect the weak; physical evolution has stopped; intellectual evolution is being stifled. Intellectual evolution is aimed at intellectual progression, extension of the individual intelligence beyond the societal intelligence. One cannot deny that any individual intelligence is in fact based upon the societal intelligence but progression can only occur via the individual. Many factors tend to create a static situation. The principle of least effort applies to all of us in some degree; intellectual effort is infinitely more difficult than physical effort and few of us take to either. Then

as another factor, the relative ease of acquisition of analytical knowledge is the deceptive siren luring most men to a life of intellectual laziness. It is comparatively easy to accumulate a fund of analytical data; this is largely a feat of memory. If this accomplishment is recognized for what it is—the first step toward knowledge—then it is fine but if the accumulation of analytical data is regarded as the end then it is evil. In my daily world, I come in contact with many persons who are basically accountants and that is a most worthy sphere of activity but the accountant never understands the significance of the numbers with which he constantly deals. To be sure the accountant assembles numbers into statistics but he never really understands statistics. Fundamental knowledge of the integrative aspects of mathematics—an understanding of the philosophy of mathematics is essential to comprehension of the limitations of the analytical information normally brought to the consciousness of the accountant. In the modern world of the accountant, he has become exposed to “business machines.” To the analyst, the machine is no more than a gadget into which you stuff properly designed coded information in the form of cards and out of the other end comes the simpler answers related to business control. To the integrative scientists in this sphere, to the cybernetician, the “business machine” is but the simplest of the mechanico-electrical systems which can be designed to usurp specific human functions. To the accountant, this specific machine is supplied with a stack of cards with holes in them; to the cybernetician, the concept is that of a message which is a discrete or continuous sequence of measurable events distributed in time.

The scientific dilemma then is the necessity for greater emphasis on integration in a world dedicated to the comparative simplicities of analysis. The scientific dilemma is also the problem of the vast mass of analytical data and the difficulty of comprehension of some portion of that data which is essential to integration. I have often made the statement that Pasteur's knowledge of science equalled that of a high school student of today who has just finished a course in general science. This statement in fact pays a great compliment to Pasteur. The totality of the societal intelligence today is immense and the individual must struggle for years to achieve reasonable rapport with science. The period of apprenticeship is being extended by both aspects of the dilemma; it is more difficult to comprehend the enormous masses of analytical detail and the integrated concepts are in many spheres so few in number as to offer little in the way of fore-

shortening the time element in the acquisition of knowledge. Unfortunately, there are no shortcuts. There is no mechanism whereby basic knowledge can be acquired by osmosis; the process is a long and tedious one and our society is aimed in another direction. In general, the evolution of the individual intelligence is related to a period of grand ambitions in which the total scope of human knowledge is the goal. Then with most, as time passes, some tiny detail of the totality becomes the dominant goal. This imperceptible passage from a degree of integrative capacity to acceptance of only a fragment of analytical detail is plain, ordinary, everyday laziness. If knowledge is the mistress it should be, there never can be the slightest slackening in the arduous pursuit. The passage of time must not dim the fervor, rather it must intensify. There can be no acceptance of a single face on this mistress, the entire field must be played. It has been said that fidelity in society is due to lack of courage and lack of energy. In science, there can be no fidelity, no dedication to any given idea, concept or thought. Everything must be held suspect.

The most monstrous things in the world are those still necessary textbooks. The textbook is a strange kind of device created for the transmission of knowledge but which represents the beauty of natural science and philosophy filtered through the inadequate brains of individuals dedicated to detail. The magnificent flights of imagination that create scientific thought are generally as foreign to these bookkeepers of science as was the artistic magnificence of ancient Rome to the Hun invader from the north. The textbook must be regarded not as the final word but as a record of thought current at some point in history. No textbook can possibly be current; the instructor must contribute currency and so often one finds the instructor reading the textbook the day before the class gets there. In some ways, it is the textbook that presents the autopsy record but it is the instructor who must put life into the corpse. Intellectual stagnation is the only possible result of textbook thinking.

The most recent scientific revolution in which I have been involved, that of clinical enzymology, is a direct refutation of everything that has ever been said or is being said in a textbook. Every advance must necessarily be such. Thus not only must analytical data be viewed as a temporary structure, but even more, must the integrative thought be viewed as an evolutionary passage from the specific to the more general. Not infrequently that which is viewed today as the generality becomes the more specific example of the

greater generality of tomorrow. There must be analysis but for the future, above all else, there must be integration and both of these pillars and simultaneously, horns of the scientific dilemma, must be regarded in their true light—not as the final word, which will probably never be uttered by man, but rather as signposts and signal lights on the road to the intellectual future.

Presently, attempts are being made to bring about integrative thinking. Cybernetics is one such endeavor, and a quite magnificent one. Another is the study of general systems theory as created by Bertalanffy. The jealously guarded boundaries of small spheres of activity must be eliminated. Scientific internationalism must be both literal and figurative. The physicist should not object to an invasion of his formerly sacrosanct domain by the biologist. Contributions have been made by physicists to biology and by biologists to physics. There can be no sharp limits, only the gradual blending of one aspect into the other.

A new type of ignorance has become a problem in the scientific world. It is that ignorance born of too much detailed knowledge. To be able to name and give the properties of each element in the periodic table is not important; to construct a periodic table is of the greatest importance. The human brain can contain just so much analytical data but there is no limit to its power if the analytical data is part of an integrated structure of total concepts. Don't worry too much about detail. It is far better to know where to find detailed knowledge than to carry it around in your head. I don't advise this policy for your next practical examination in subject X, but for intellectual progression I do recommend it.

Creativity is the important element in all human endeavor and the only path to creativity lies in integration. The significant track of intellectual integration and creativity can easily be covered by the dust of unimportant fragments of analytical knowledge. It is far more important to know one generalization than to know all of the detail upon which that generalization rests. And I might add it is much easier on the creative mind. The analogy of creativity and the deep well into which are thrown many things is excellent, but whether or not something bounces back out of the deep well depends upon retention of a degree of elasticity in the entire system, elasticity is orientation toward integration.

At the present time, much emphasis is being put upon the study of creativity itself. There are different layers of creativity. The arts

deal with creativity in a system related entirely to sensory perception. The stimulus to creativity in the arts is sensory, the dedication or study period is sensory, and the product is for sensory perception. From beginning to end, the senses are the determinant factor. For this reason, creativity in the arts can be related to pathology. Van Gogh could create a great painting while completely psychotic; Coleridge could create great poetry while under the influence of drugs; Poe could create while totally alcoholic; but you cannot create great integrative thought in natural science in a parallel manner. To be sure, the measurements we make in science are an extrapolation of sensory perception but once those measurements are made their significance is no longer determined by sensory mechanisms but rather by association areas in the brain. I know of no single instance in which great science has come out of individuals who were pathological. It is often stated that Kekule created the concept of the benzene ring while in an alcoholic daze in which he dreamed of six snakes arranging themselves in a hexagonal pattern but there seems little basic reason to accept this story. The ring concept has been called "the most brilliant piece of prediction to be found in the whole range of organic chemistry" and it is doubtful that it was created under the influence of a straight chain carbon compound with a hydroxyl attached.

Recently, a fascinating study was carried out with lysergic acid diethylamide—the so-called hallucinogenic drug—in which recognized artists were caused to paint while under the influence of the drug. The product of these artists while drugged and while completely normal was then submitted to a panel of art experts. In every case, the work of the artist carried out under the influence of the drug was judged to be superior. This is confirmation of the purely sensory aspect of creativity in the arts. Unfortunately, it will be most difficult to conduct a parallel experiment with scientists but I doubt that it would reveal an increased integrative capacity unless the subject were an analyst. In the latter case, elimination of the forces binding the mind to the trough of analysis might result in some rather amazing flights of creativity. In fact, one wonders if psychological procedure might not be devised involving testing under normal conditions and under the influence of the diethylamide of lysergic acid. These tests would reveal the degree to which the individual was bound down in his thinking by tradition, by routine or by analysis. Any individual so restricted would then in the scheme of the social system be oriented toward studies permitting liberation from such thought restraints.

In everyday living and particularly in the political world, the necessity for integrative thinking becomes obvious. The American public elects its representatives by a limited type of analytical thinking. Generally, the issues determinant in elections are highly personalized and the result is that the election becomes a popularity contest. This is a defect in the democratic system which would be corrected by orientation of the electorate toward integrative thought. How many persons do you know who will discuss any political figure in a purely dissociated manner? Ninety-nine percent of the population will consider the political figure from the standpoint of the limitation of analysis and the personal self-interest factor. It is interesting to speculate on the discussion between a member of the United States Chamber of Commerce and a representative of the new conjoined labor front on the relative merits of the probable Republican and Democratic candidates for the Presidency. Believe me, it would not be integrative, perhaps not even analytical, but surely explosive.

Since the dawn of consciousness in man, he has eternally sought some answer to the question "What is the purpose of mankind?" It would seem that a partial answer to this lies in the statement that the purpose of mankind is intellectual progression. It is not an easy path. The majority today even resent that path. Intolerance of the intellectual is more prevalent than ever before. This is due both to a failure on the part of the nation and on the part of the intellectual. The nation must realize that its very existence is increasingly dependent upon the intellectual and in turn the intellectual must come to realize his social responsibilities. Unfortunately, governmental regulations cannot provide the milieu for creativity but such regulations can ease a difficult path. Today, in Russia, an effort is being made to provide a reservoir of technicians and scientists by offering as an alternative a Siberian vacation. While this approach has merit to provide the lower echelons of technical brains, it is no approach to true creativity. The public must be educated to respond to the creative mind and the creative mind must become attuned to the public. Distrust has arisen toward science because the most recent manifestations of science as it affects the public are inherently destructive. Anti-intellectualism, however, has existed since the dawn of man's history. Correction of this unfortunate problem relates in the greater sense to the publicly recognized integration of the totality of science into the social structure. Resolution of the problem presented by scientific dilemma will circumvent the current impasse. The purpose of man is intellectual

progression and this can only be achieved by integrative thinking at all levels.

It is not my place to say that science cannot be a sacred cow. There are as many defects in its structure as in any other but we often refuse to recognize their existence. In the last centuries science has challenged philosophy and religion and in every encounter has won. Today, with a somewhat red face we are forced, out of truly integrative thinking, to acceptance of indeterminability. This places the solid house of science on a foundation of sand and the flimsy tent of philosophy and religion on a foundation of stone. The answer must lie in integration of all aspects of human endeavor, of all facets of human knowledge, of all strands of man's dreams. The significance of any fragment, even the reality of any fragment of knowledge, relates entirely to its integration into the totality of human knowledge. Science should be relegated to its proper position in the hierarchy of the intellect at the feet of a greater structure, natural philosophy. The latter is integration in its finest form, and is all-encompassing. In this greater pattern, recognition of the scientific dilemma of analysis versus integration can be made the sounding call to the attack and ultimate defeat of ignorance, bigotry, intolerance, disease and possibly even death.

## METHYL CELLULOSE AS A TROCHE BASE

By G. F. Trotter,\* D. B. Hawkins, and E. L. Parrott

THE use of a medicament to be slowly dissolved in the mouth providing a prolonged release of a therapeutic agent is not new to pharmacy. Troches reached the peak of their popularity in the U. S. P. VI, which contained 16 monographs of troches, and declined until all troches were deleted from the U. S. P. by the Eleventh Revision, and from the National Formulary by 1942.

With the development and use of antibiotics in every conceivable form, it is not surprising that troches reappeared as Penicillin Troches in the U. S. P. XIII, and that two troches are now official in the N. F.

With the demands of production, the older molding method of troche manufacture has been largely replaced by the compression method. Troches are, in fact, tablets made so that they dissolve slowly. The conventional modes of tablet production, either the wet granulation or the precompression method, may be used to produce troches; however, no disintegrating agents are employed and a formula is chosen to give a tablet which will dissolve slowly. Thus, in addition to being compressible into a firm elegant tablet which is easily ejected, the formulation must have free flowing characteristics and strong adhesive properties.

Sugar with binding agents such as the natural gums or gelatin is the more common troche base. It was felt that perhaps this base could be improved by utilizing other inert substances, which might eliminate granulation and produce a more viscid liquid upon dissolving. The more viscid liquid would maintain the drug in contact with the mucosal surface by offering greater resistance to being washed away by the salivary secretions.

The use of methyl cellulose solution as a binder in tablets and as a tablet ingredient suggested that it be investigated as the main ingredient of a troche. Numerous investigators have demonstrated the physical and pharmacological acceptability of methyl cellulose for pharmaceutical formulation (1, 2, 3, 4).

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\* The paper is based on a thesis submitted by Gerard F. Trotter to the College of Pharmacy of the University of Arizona in partial fulfillment of the requirements for the degree of Master of Science.

### Preparation of Troches

Seven viscosity types—15, 25, 50, 100, 400, 1500 and 4000 cps—of methyl cellulose were used in this study. A Stokes single punch tablet machine with a half-inch standard concave punch was used throughout the experimental work. As far as practical the pressure in making the troches was kept constant.

**Wet Granulation.**—All samples of the methyl cellulose were dried at 40° C. A binding agent was added and the wet granulation was passed through an 8 mesh screen. After drying at 35° C. in an oven, the granulation was passed through a 14 mesh screen, 3% calcium stearate was added as a lubricant, and the mixture was compressed.

This procedure was carried out on the seven viscosity types of methyl cellulose using as a granulating solution: (a) distilled water, (b) 2% methyl cellulose solution of the corresponding viscosity type, and (c) 50% glucose solution. These troches were found to crumble when only a slight pressure was applied. It was thought that the addition of sugar to the methyl cellulose might produce a harder troche.

The wet granulation procedure for the seven viscosity types was repeated using 25, 50 and 60% powdered sugar. As the troches made by these formulas using the wet granulation method were also soft and lacked a smooth uniform appearance, it seemed best to abandon the wet granulation method.

**Direct Compression.**—An unsuccessful attempt was made to compress the powdered methyl cellulose directly without any pretreatment or lubricant. Various lubricants—2% talc, 3% calcium stearate, and 3% stearic acid—were mixed with the methyl cellulose, and the powder was compressed. Difficulty was encountered with the free flow of the powders into the die cavity, and the subsequent ejection of the troche. The troches were not as hard as desired.

In attempting to produce a harder troche, 25% superfine sugar and a 5% magnesium trisilicate lubricant was added to the methyl cellulose. This formula seemed more satisfactory. The lower viscosity types of methyl cellulose appeared to give the more satisfactory troches with this formula (Table I).

**Control.**—To serve as a standard for comparison two sugar base troches were compressed under similar conditions. The formulas were:

PSG-T 1 (5)		
Powdered sugar		435.0 gms.
50% glucose solution	q.s.	
Calcium stearate		4.5 gms.
SA-T 1 (6)		
Sugar		465.0 gms.
Powdered acacia		15.4 gms.
20% acacia solution	q.s.	
Talc		15.4 gms.

TABLE I

COMPRESSIONAL CHARACTERISTICS OF METHYL CELLULOSE TROCHE FORMULAS

Type	Flow	Compression	Ejection	Appearance of Troche
15 cps	Good	Hard troche	Good	Smooth
25	Good	Hard troche	Good	Smooth
50	Good	Hard troche	Good	Smooth
100	Poor	Hard troche with greater pressure	Good	Smooth
400	Very poor	Not readily compressible	Very poor	Rough
1500	Very poor	Not readily compressible	Very poor	Rough
4000	Very poor	Not readily compressible	Very poor	Rough

### Evaluation

Of the troches produced from 70% methyl cellulose, 25% superfine sugar and 5% magnesium trisilicate, those containing the lower viscosity type methyl cellulose appeared to be most suitable. In vivo and in vitro evaluations of the troches containing 15, 25, 50 and 100 cps methyl cellulose were carried out.

**Hardness.**—Hardness generally is considered a measure of the mechanical resistance of tablets to any breaking or attrition process (7). The action that a troche held in the mouth undergoes is an abrasive or attritious process, and the harder the troche the more resistant one would presume it would be to this action.

A Strong-Cobb tablet hardness tester was used to obtain an indication of the hardness of various troches. Forty troches of each type were selected at random and the average hardness was measured (Table II). It can be seen that the methyl cellulose troches are much more resistant to crushing than the sugar base troches.

TABLE II  
HARDNESS OF VARIOUS TROCHE BASES

Type Troche	MC-T 15	MC-T 25	MC-T 50	MC-T 100	PSG-T 1	SA-T 1
Average Gauge Reading	28	28	25	23	16	5
Per Centage Broken At Average Gauge Reading	0	0	30	60	100	100

**Drug Release.**—A colorimetric assay was adopted to determine the amount of phenolsulfonphthalein released at various intervals from the troches being evaluated. Troches were compressed from a mixture containing 0.1% phenolsulfonphthalein so that each troche contained approximately 0.5 mg. of dye. A dozen of these troches were selected at random and placed in 30 ml. of distilled water in a flask being agitated at a constant temperature of 37° C. At five minute intervals a sample was withdrawn and analyzed (Lumetron Photoelectric Colorimeter). To the troches that had been drained, another 30 ml. of distilled water was added, and the procedure was repeated.

As the sugar base troches dissolved faster, a one minute and a forty-five second interval were employed for the PSG-T 1 and SA-T 1 troches, respectively.

In all cases a blank was run with troches of corresponding formula that contained no dye. A series of five determinations were made for each viscosity type. A compilation of the data is shown graphically in Fig. 1. It is apparent that the methyl cellulose troches released the dye about one-tenth as fast as the sugar bases because of the slow dissolution of the methyl cellulose troche. A comparison of the different viscosity types methyl cellulose troches and the amount of dye released was made (Fig. 2).

**Viscosity.**—One would anticipate that with an increase in viscosity of the oral fluid caused by the dissolving troche, the drug would be held and allowed to act at the site of dissolution for a longer time.

Using the same apparatus employed in determining the release of dye from the troches, fifty troches were shaken at 37° C. with 125 ml. of distilled water for 2½ minutes, at which time, samples were withdrawn, and the viscosities measured (Ostwald-Fenske viscometer).

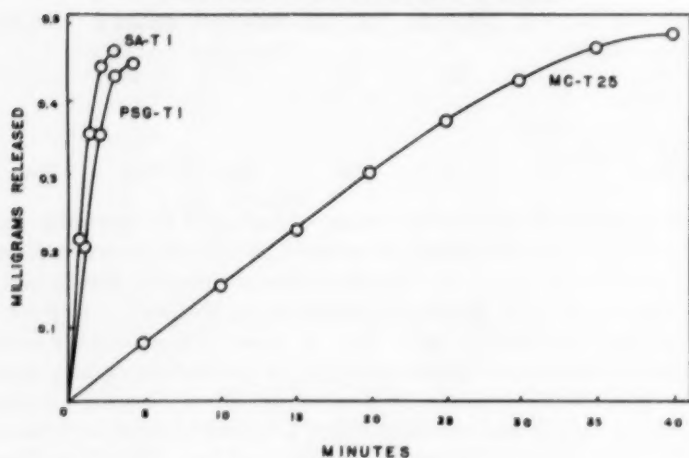
RELEASE OF PHENOLSULFONPHTHALEIN FROM  
METHYL CELLULOSE AND SUGAR TROCHES

FIGURE 1.

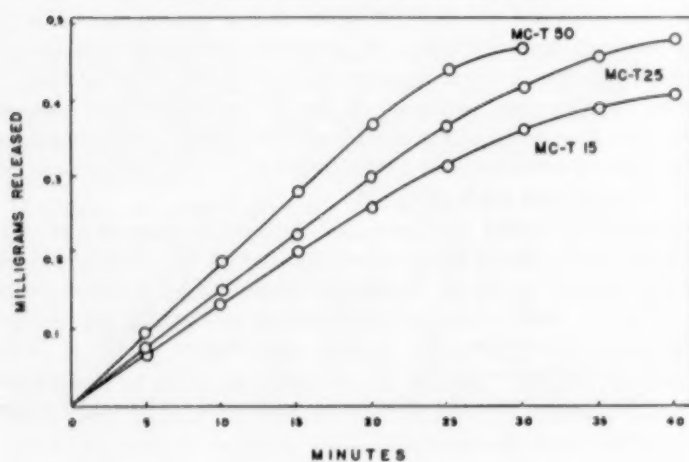
RELEASE OF PHENOLSULFONPHTHALEIN FROM VARIOUS  
VISCOSITY TYPE METHYL CELLULOSE TROCHES

FIGURE 2.

The viscosities of the solutions show that the methyl cellulose troches all produce solutions of a higher viscosity than the sugar base troches (Table III).

TABLE III

VISCOSITY OF AQUEOUS PHASE AFTER SHAKING WITH TROCHES  
FOR 2½ MINUTES

Type Troche	MC-T 15	MC-T 25	MC-T 50	MC-T 100	PSG-T 1	SA-T 1
Centipoises	1.993	2.295	2.418	17.838	0.891	1.080

**Dissolution Time.**—The approximate time of dissolution was determined by in vitro and in vivo studies. A troche was placed in 90 ml. of distilled water in a shaking flask at a constant temperature of 37° C., and the time of dissolution was observed.

A group of 30 students was given samples of troches with instructions to place the troche on the tongue and allow it to dissolve. In each group of 30, five individuals were testing the same troche formula.

A comparison of these tests shows that the methyl cellulose troche requires approximately ten times as long to dissolve as the sugar base troche (Table IV).

TABLE IV.—DISSOLUTION TIME OF TROCHES

Type Troche		In vivo	In vitro
MC-T	15	51 minutes	30 minutes
MC-T	25	53	35
MC-T	50	30	28
MC-T	100	53	28
PSG-T	1	4.5	3
SA-T	1	4.4	2.5

### Summary

1. A formula for a methyl cellulose troche that may be made by direct compression is presented.
2. The methyl cellulose troches were harder and released an incorporated dye more slowly than the sugar base troche.

3. By both in vivo and in vitro studies, the methyl cellulose troches were found to dissolve about one-tenth as rapidly as the sugar base troches.

4. The methyl cellulose troche as it dissolved increased the viscosity tending to hold the drug in contact with the oral mucosa for a longer period.

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## DETERGENT RESEARCH RELATED TO WATER AND SEWAGE TREATMENT \*

By F. J. Coughlin \*\*

THIS is the first report on the research activities sponsored by the Association of American Soap & Glycerine Producers related to questions which are raised about detergents in some water supply and sewage treatment situations. The report will be of special interest to the members of the Association who manufacture detergents and detergent raw materials. The Association's research activities have been handled by several technical committees under the guidance of the Technical Advisory Committee with L. H. Flett of the National Aniline Division, Allied Chemical & Dye Corporation as Chairman. It is well-nigh impossible to do justice to the efforts of the individuals and companies participating in this work and to the spirit of cooperation which has been shown.

### *Questions Raised*

Requirements for water are constantly increasing, both for household and industrial use. Consideration of the problem of adequate future water supplies raises questions about the proper disposal of all types of waste, including domestic sewage. One approach to the waste disposal problem is through the research and other programs which are being set up by industry and by Federal, State, and local agencies. Our industry is proud to take a part in this broad program.

For some time now water supply and sewage treatment people have shown interest in detergents. This interest seems to lie in the possible effects, if any, of the normal use of detergents on water supplies and in sewage treatment plants. Detergents are sometimes associated with problems of frothing, sedimentation, and coagulation difficulties in water treatment plants. In the treatment and disposal of domestic sewage, the normal use of detergents is said, in some instances, to cause frothing and to retard the biological processes

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\*\* Chairman, Technical Advisory Sub-Committee on Research of the Association of American Soap & Glycerine Producers, Inc.

of decomposition. The Association's research program undertakes to determine whether there is any connection between the difficulties reported and the normal use of detergents, and, if so, to what extent. These problems had existed before the advent of detergents and it would be expected that they would increase in severity as the population increases.

The interest of our industry in cooperating in the solution of water supply and waste water disposal problems goes back a good many years and our Association and industry want to play our part in attempting to determine the facts and ease the problem. The industry is glad to have a common interest in these problems with many able and conscientious groups, including the sewage and water treatment operators, the sanitary engineers and chemists involved in water supply and waste water disposal, the Federation of Sewage & Industrial Wastes Association, the American Water Works Association, the U. S. Public Health Service, and the Ohio River Valley Water Sanitation Commission, known for short as Orsanco.

Some of the people interested say that detergents are causing no difficulty. Going to the other extreme, the opinion is also expressed that detergents are causing difficulties now and are likely to cause further difficulties in the future. The most frequently expressed opinion seems to be that the information available does not give cause for major concern and that steps should be taken to obtain additional facts to answer the questions raised. This appears to be the thinking of U. S. P. H. and Orsanco and expresses the attitude of the Soap Association Technical Committee.

Until the time when satisfactory answers to all these questions are available, our industry will wish to take sound constructive action and cooperate with others as a matter of broad public responsibility in seeking the possible solutions to these difficult problems.

#### *Definitions and Technical Information Regarding Detergents*

By way of definition, the term "detergent" is used in this discussion to refer to the complete product as it is found in the package on the grocery shelf or in barrels or drums for general bulk industrial uses. In homes, detergents have grown to where their sales are well over half the total of all washing products. Detergents contain surface active agents sometimes referred to as surfactants, and in addition they may contain inorganic and organic builders. Of the surface active agents, alkyl benzene sulfonate, a derivative of petroleum, often

referred to as ABS, is used more extensively than any other. The most important builders used are the complex phosphates.

For those interested in further information on the characteristics and behavior of detergents, papers by Haney (1), Gowdy (2), and Hoyt and Flett (3), are recommended as they pertain to water and sewage treatment questions. The significance of the quantitative aspects of the behavior of detergents is not always recognized. At extremely low concentrations, detergents do not possess the same characteristics—such as foaming ability or emulsifying properties—which they show at the higher concentrations suitable for cleaning purposes.

To obtain the kind of suds that the housewife likes in her dishpan, she may use about 3,000 parts per million or three-tenths of one percent of the packaged synthetic detergents. This would be equivalent to about six hundred parts per million or six-hundredths of one percent of surfactant.

Typical concentrations of detergent likely to be present in domestic sewage have been reported by Haney with 53 parts per million as the highest value (1). This would be equivalent to ten to fifteen ppm of surface active agent, assuming, for the purposes of obtaining a maximum figure, no decomposition or die-away. The concentration of surface active agent present in surface waters would therefore be considerably lower because of dilution effects, and in some instances might be zero. Some of the difficulties in water treatment have been attributed to as little as one to four parts per million of detergent.

Now to give you an idea of just how small one part per million is, one pound in five hundred tons is one part per million—or one 1¼ pound package of household detergent in 150,000 gallons of water is one part per million. 150,000 gallons of water would just about fill a tank 20 feet in diameter and 65 feet high. It is remarkable that methods can be developed to find such trace quantities.

One manifestation of the technical interest in this problem has been the development of a certain amount of literature which associates detergents with the difficulties encountered. Examined critically in the light of the chemistry and behavior of detergents, it is apparent that proof has not been established that detergents necessarily create any ill effects. Also, it is quite evident that other factors might have caused the adverse effects which have been reported and further it

could very well turn out, when all the facts are in, that detergents do not produce the difficulties for which they are blamed.

### *Frothing in Sewage Treatment*

Foam first reared its frothy head in sewage treatment plants long before the advent of detergents. Now, when the froth develops to photogenic heights, it is likely to receive considerable newspaper publicity which more frequently than not associates it with detergents. In 1947, references to frothing in sewage treatment plants began to appear in the technical literature and the trade press, and there was some speculation then about whether or not detergents might be the cause. However, it was assumed that sewage plants would be able to handle the relatively small amounts of detergents which would find their way into sewage even if usage was at a maximum. This seemed reasonable since frothing had occurred before the introduction of detergents, and since there are many other foaming agents which might very well be present in sewage or could be produced during the oxidation and decomposition of the sewage.

The first opportunity for the soap industry to offer help in a specific situation came early in 1951. At that time, a sewage treatment works developed a froth about eight feet high. Naturally, in Texas! San Antonio, to be exact.

There were no methods of analysis to determine how much detergent was present in the sewage or to evaluate the possible breakdown of detergents during treatment. San Antonio proceeded to make a study of their problem in which Procter & Gamble cooperated (4, 5). Experiments showed that the froth could be produced or it could be made to disappear at will simply by lowering or raising the amount of activated sludge solids re-circulated through the aeration tanks. Furthermore, from detergent usage and from the amount of sewage treated, the San Antonio people calculated the quantity of detergents that might be present in the sewage. The concentration was so low that it was not conceivably capable of producing the kind of froth which developed.

With two hundred parts per million (two-hundredths of one percent) of suspended solids, which is a low level in the aeration tanks, the frothing difficulty occurred. This froth was made to disappear through the simple expedient of raising the suspended activated sludge solids above a critical level of about 1400 ppm. At a

high solids level of thirty-five hundred parts per million, or roughly, four-tenths of one percent, even as much as two hundred and fifty parts per million of packaged detergent product did not create frothing. From this and much more evidence obtained in the San Antonio tests, it was reasonable to conclude that at least in this instance synthetic detergents were not responsible for the frothing troubles.

The principles developed at San Antonio were then verified at a smaller plant located at Bryan, Ohio, which operated under different conditions than that at San Antonio. Several detergent brands were added to the aeration tanks at Bryan. In all cases, the addition of detergent to the tanks did not change the frothing picture.

Observations indicate that not many sewage works encounter a significant froth on their aeration tanks, although some plants do experience a slight continuous foam, which apparently is not extensive enough to cause trouble. It seems to be an unusual situation when the froth grows to troublesome heights. Sewage treatment people are developing methods for controlling frothing, independent of what might be the cause.

It seems premature for anyone to conclude that detergents should shoulder the blame for this frothing. It would be about as logical as concluding that detergents cause the foam on beer, in the case where a small granule of detergent had been added to a glass of beer. While it is true that detergents are used extensively, are good foamers, and produce froth at high concentrations, these reasons hardly seem to be sufficient to justify the conclusion that they cause the froth in sewage treatment plants. It is apparent, of course, that other foaming agents—and there are many of them—are present in sewage.

The San Antonio experience was followed by difficulties which occurred a little later in New York, Philadelphia and Los Angeles and which were featured on the front pages of the newspapers. In this period there were more frequent references in the trade and technical press to detergents as the possible cause of the frothing in sewage works. Thus, it became obvious that something more should be done, if the industry did not want the public to accept by default the unproved assumption that detergents were to blame.

#### *Biological Degradation*

The frothing experiences in sewage works led to some apprehension and speculation to the effect that some of the detergent com-

ponents, particularly ABS, might be stable enough to resist decomposition and breakdown in sewage treatment and might pass on unchanged into surface waters, such as rivers and lakes. These apprehensions arose even though lack of sound analytical procedures made it impossible to obtain reliable objective measurements. Thus, there was no real proof that such things were happening.

The California Research Corporation saw the importance of developing fundamental information on the fate of ABS in sewage treatment processes and undertook a practical scale study. An unequivocal method of analysis was used, employing ABS tagged with radioactive sulfur. This work reported by House and Fries at the New York Sewage and Industrial Waste Association meeting in New York City on January 19, 1956 shows that in the activated sludge plant in which the tests were made, eighty to ninety percent of the ABS was destroyed by the normal sewage treatment process. This is the same efficiency as obtained on normal sewage in this plant.

#### *Analysis of ABS*

In view of the fact that methods of analysis for the extremely low concentrations of ABS or other surfactants in water and sewage were inadequate, it was soon apparent that an analytical method which would give reliable results was needed in order to determine the extent of the problem.

A method known as the Methylene Blue procedure has been used rather generally in the past and it is only recently that its weaknesses are coming to be recognized. Unfortunately, many people have relied on the Methylene Blue method and quite a bit of literature is based on it. It is far from satisfactory because urine, tea, coffee, and distilled water extracts of such materials as straw, leaves, and rotted wood—all of which contain natural surfactants—appear by this method to contain ABS when, in fact, it is not there. The A. W. W. A. Task Force Report (1) points out that the natural production of surface active agents is considerable and that raw waters may be expected to contain a variety of natural surfactants.

Of course, the Methylene Blue method is still suitable where a quantitative result is not essential and when the concentration of ABS is obviously so low that it is insignificant. For example, using this method which may give fictitiously high values, the Ohio River at Anderson Ferry, Ohio, has been ranging from about two-

hundredths of one part per million to fifty-six hundredths of one part per million, based on three samples per week over the past year. Even if the entire amount of "apparent ABS" were real, there is no need for checking the Ohio by more laborious and time-consuming methods.

To develop a reliable method of analysis which is unaffected by interfering substances is the mission of the Soap Association's Sub-Committee on the Analysis of ABS. Such a method will not only make it possible to deal with the problem in a quantitative way but will be a basic tool for further research.

In giving top priority to the analytical problem, the Soap Association Technical Committee is following the suggestions of the Ohio River Valley Water Sanitation Commission and the American Water Works Association Task Group on Detergents.

As a matter of fact, the Ohio River Valley Water Sanitation Commission's interest in the possible effects of detergents stimulated the formation of the present Soap Association Sub-Committee on the Analysis of ABS. Orsanco set up a Detergent Sub-Committee as part of the Chemical Industry Advisory Committee. This Sub-Committee, in turn, invited companies engaged in the manufacture of detergents and detergent raw materials to cooperate in the development of a valid analytical method. The U. S. Public Health Service at the Taft Engineering Center in Cincinnati also was invited to join in the project. For a while this group proceeded on an informal basis. Later on, since all the industry members of the informal group were members of the Soap Association, it was a natural move for them to become an official committee sponsored by our Association. The Soap Association committee has had five meetings in the past two years and it is estimated that the ten committee members have spent over 17,500 man hours on laboratory tests and experiments. The new analytical method should be considered a noteworthy accomplishment.

To make a long and highly technical story as short and as non-technical as possible, the new method involves the measurement of the amount of ABS in the sample in question, first by removal of the ABS by adsorption on activated carbon. This begins to sort out the ABS from the larger amounts of other organic matter present. Then the ABS is removed from the carbon column and next a further sorting out by chemical methods is accomplished. When a sufficiently

large quantity of pure ABS has been quantitatively obtained from the sample, the final step is to measure it qualitatively and quantitatively by the use of an infrared spectrophotometer. This new method, checked out carefully by the committee, should soon be ready for publication.

The Soap Association technical group is the first to recognize that the method as it has been evolved will not be practical for the average sewage works or water treatment operator to use routinely. A simpler method for making routine analyses is still needed and we hope to come up with something on this, too. The Taft Sanitary Engineering Center of the U. S. Public Health, has reported on a new colorimetric short procedure called the "Methyl Green" method. The Monsanto Laboratories have also been doing some work in this field and are about ready to report on another short method. The study of shorter methods will continue to be an important part of our future program.

#### *Water Treatment*

In the water treatment area, the need for a more active program became apparent when the quiet on the waterfront was disturbed at Wheeling, West Virginia, around Thanksgiving of 1953. Large quantities of froth formed on the Ohio River and in the water treatment plant there. The froth was accompanied by bad taste, discoloration, and extreme difficulty with filtering and settling. The river had been at an extremely low stage and almost in pool. This low flow brought about the presence of high concentrations of various organic and inorganic substances in the river water. When frothing occurred, the river water appeared to contain about one part per million of "apparent ABS," using the Methylene Blue procedure which includes the amounts of any interfering substances present.

With such a low level of ABS in the water, it was extremely difficult for anyone to postulate how detergents might have produced the foam. On the other hand, the foam contained a high concentration of ABS which was present chiefly on finely divided solids held and suspended in the foam. This, while difficult to explain, was still not conclusive. Since that time, incoming water with the same concentration of ABS by the Methylene Blue method has been treated by the water works at Wheeling without any trouble. In

retrospect, a fair and reasonable point of view seems to be that detergents from domestic sewage were not the principal cause of the Wheeling froth, if indeed they had any appreciable effect at all.

### *Phosphates*

More recently, in instances where water treatment plants have encountered difficulties with coagulation and sedimentation, there has been some speculation that the complex phosphates from household detergents might be involved.

It is true that if enough complex phosphates are present, they could retard coagulation and sedimentation in water treatment. In fact, it is because of this particular property that these materials have become such an important constituent of household detergents. However, before the conclusion is reached that they cause such troubles, there should be an answer to the question: "Are the complex phosphates or other phosphates present in sufficient concentration in the surface waters going into the water treatment plants in question to produce the effects reported?"

It is difficult to measure the possible effects of the complex phosphates from the household use of detergents on water treatment processes. The reason is that the complex phosphates undergo changes during the washing process itself, during their travel through the sewers, and in the sewage works. Furthermore, any residue which passes on to surface waters is expected to undergo further changes because the phosphates are susceptible to being decomposed by the plant and animal systems present in all surface waters.

There are many other unanswered questions. For example, "What are the conversion products, if any, which reach the water treatment plants?" "How quickly do the complex phosphates revert to the simpler forms and what effect, if any, is produced by the conversion products?" "If the phosphates have any effects, how much of the effect is contributed by the phosphates from household detergents, how much by the naturally occurring organic and inorganic phosphates, how much by the phosphates from fertilizers, how much by phosphates from industrial plants, and how much from any other source?"

A Phosphate Committee was recently organized in our Association to explore questions which have been raised. This hard-working committee includes our own members and, in addition, non-member

organizations in the phosphate industry who are interested in participating. The committee has started out on the problem of establishing good methods of analysis for the types of phosphates in the low concentrations which might be found in water and sewage. H. V. Moss of Monsanto, who is an active member of several other committees in this general field, is the able and efficient Chairman of the Phosphate Committee.

#### *Kansas*

Our technical groups have already had a few opportunities to help others to investigate some of these difficult problems. After a succession of several drought years in Kansas, serious water quality problems have been encountered in various parts of the state, and there is speculation that detergents are a factor in causing the difficulties. In fact, last year a bill was introduced in the Kansas legislature which in essence would have made it unlawful to put detergents into a public sewer. Working on the principle that legislation would not solve the problem, but that research would, our Association offered its help. A representation from our Technical Advisory Sub-Committee on Research and our Committee on Analysis discussed our activities in detail with people from the Kansas State Board of Health, and a report was made at the April 1955 joint meeting of the Kansas Sewage & Industrial Wastes Association and the Kansas Section of the American Water Works Association (6). A few weeks ago, the Kansas State Board of Health people asked us to cooperate further in studying current problems and the Technical Committees have been glad to take steps to assist in the present situation.

#### *Britain*

A British Government Committee on Synthetic Detergents is at present studying the question there. The Association's activities have been reported by members of the Technical Committees to their associated companies in Britain, and in this manner the information which our Technical Committees have developed has been made available to the British Committee. It is hoped that the work which is under way in the United States may be generally applicable to the British situation and may be helpful in solving the sewage treatment problems and any water quality problems which exist over there.

*Ohio River Valley Water Sanitation Commission, Detergent Sub-Committee*

To a great extent, because of the Wheeling experience right in its own bailiwick, the Ohio River Valley Water Sanitation Commission appointed its Detergent Sub-Committee, mentioned previously. Prior to this, E. J. Cleary, Executive Director and Chief Engineer of Orsanco, had suggested a program of investigation that the Sub-Committee might consider. It is indicative of Cleary's foresight that after these suggestions were reviewed carefully by those interested in the problem, it is essentially the program which is being followed at the present time. Soon after its appointment, the Orsanco Detergent Sub-Committee extended an invitation to the Soap Association to help in the investigation of this broad industry question since it extended beyond the confines of the Ohio Valley. The Soap Association was ready and willing to cooperate and accepted the invitation. It was a natural development for the Association to take over the analytical problem as has been described and to organize and underwrite further constructive research investigations.

*Research Projects*

The Technical Advisory Sub-Committee on Research was asked to recommend the problems for study, where they should be placed, and to determine the budget required to finance the work. The Association then solicited and obtained the funds required from member and interested non-member companies.

The question as to the type of ABS to use for study was resolved by making a composite of the alkyl benzene from the four suppliers on the Sub-Committee on Research. From this composite, Wearn and Ross of Colgate have produced a composite ABS for use in the Association studies.

A system was set up where liaison with each of the projects is being handled by one or more members of the research committee, and each of the projects has been visited by members of the committee at least once this year.

Here are the four projects that have possibilities of doing a lot of good.

The first project to be placed by our Sub-Committee on Research, was at M. I. T. The Continental Oil people had been discussing with

M. I. T. the detergent problem from the point of view of possible biochemical degradation of the surface active agents. It is obvious that breakdown of the surface active agent to the point where surface activity is destroyed would probably remove it as a cause of the frothing in sewage works, and would completely eliminate the problems in water treatment associated with the surface active agents present in detergents. The work is under the direct supervision of Professor Ross E. McKinney in the Civil Engineering Department. Professors Clair N. Sawyer and Rolf Eliassen are also associated with the project.

The second project was placed at the Sanitary Engineering Research Laboratory of the University of California at Berkeley, under Professors E. S. Crosby and P. H. McGauhey. They are following up on the work of the California Research Corporation, mentioned previously, and are making a more comprehensive study, under a wider range of conditions, of the fate of ABS in sewage treatment and in surface water supplies.

The University of Wisconsin project is in charge of Professor G. A. Rohlich and L. B. Polkowski. They are working on the causes and prevention of frothing in sewage treatment plants. Frothing systems free of detergents will be studied, as well as those containing detergents. As the headlines usually associate detergents and frothing, the Association obviously has a vital interest in getting to the bottom of this problem.

The fourth project is under the supervision of Professors J. C. Dietz and R. S. Engelbrecht at the University of Illinois. It will study, as a first phase, the complex phosphate components of detergents, and later ABS, in water treatment plants. To get at the question of possible amounts that may be present in surface waters, it will survey the type and amounts of phosphates present in some of the waters in the State of Illinois, using the analytical tools supplied by the Phosphate Committee. Also, it has set up a pilot plant unit to study the settling operation in water treatment.

These research projects have been placed in excellent hands and cover the difficult areas of water and sewage about as effectively as any four projects could. These explorations, when completed, should reveal new and valuable information.

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## SELECTED ABSTRACTS

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**Riboflavin in the Formulation of Parenteral Preparations.** Brumfield, P. E., and Gross, H. M. *Drug & Cosm. Ind.* 77:46 (1955).

The authors presented a comprehensive study of the formulation characteristics of riboflavin. A number of interesting and useful facts were presented.

Riboflavin exists in three crystal forms, each having different physical properties. A number of derivatives have been prepared in an effort to increase the solubility and stability of the vitamin. Of these, riboflavin-5'-phosphate and methylol riboflavin hold considerable promise.

Because of the low solubility of riboflavin in water many solubilizers have been investigated. Data is given on a list of 40 solubilizers. Some are not active in the pH range necessary for multivitamin preparations (pH 3.5-5.0), others produce dark colored compounds. At present the most acceptable solubilizer is N-(2-hydroxyethyl) gentisamide.

The more acceptable bacteriostatic agents were discussed, including, chlorobutanol, phenol, benzyl alcohol, p-hydroxybenzoic acid esters, and gentisic acid. All of these may be used effectively within the limitations or conditions discussed.

In the presence of ascorbic acid, riboflavin and ascorbic acid produce mutual destruction. Additives such as thiourea, glutathione and albumin tend to decrease these reactions. Thiourea may also decrease the interaction of thiamine and riboflavin. Niacinamide is a valuable solubilizer for riboflavin and, in lyophilized material, it improves the sturdiness and uniformity of crystal size of the cake. Calcium inactivates riboflavin and some of the other vitamins. Therefore, panthenol is preferred to calcium pantothenate. Cyanocobalmin is also apparently inactivated to some degree by riboflavin. Riboflavin-5-phosphate is decomposed rather rapidly in the presence of a number of metal ions, in even trace quantities.

A procedure for the preparation of multivitamin solutions is outlined by the authors.

**Prednisolone in the Treatment of Leukemia in the Adult.**

Hill, J. A. Presented before the Graduate Symposium on Geriatric Medicine, New York City, Dec. 1, 1955, sponsored by the American Geriatrics Society. Massive doses of prednisolone (or prednisone), ranging from 250 to 5000 mg. a day, were given to 21 patients with acute leukemia, 6 with chronic lymphatic leukemia, 1 with Hodgkin's Disease, and 4 with lymphosarcoma. Therapy was continued for periods up to three weeks. No serious or irreversible side effects relative to elevation of blood sugar or changes in the sodium and potassium content of the blood were observed.

The therapy with massive doses of these steroids was found useful in three phases of acute leukemia: (1) in the acutely ill patient where antimetabolite drugs did not have time to take effect; (2) in cases in whom remissions appeared to be unduly delayed after sufficient courses of antimetabolites; and (3) in those patients in the terminal phase in whom all other therapies had ceased to be effective.

Prior to the advent of 6-mercaptopurine, azaserine and massive steroid therapy, only 13 per cent of acute leukemia patients in the area serviced by the author survived beyond one year. Since these drugs have become available, 38 per cent have survived beyond one year. Among acute lymphatic leukemia patients, the 12-month survival rate has increased from 21 to 66 per cent. Patients with acute granulocytic and monocytic leukemia who survived beyond 12 months increased from 7 to 34 in every 100 patients. In addition, the remission rates during the same periods showed an overall improvement from 41 per cent to 86 per cent.

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**The Evaluation of Hydrocortisone Ointment in Dermatoses.**

Mullins, J. F., and Shapiro, E. M. *GP* 12:59 (Nov. 1955). The local application of hydrocortisone acetate and hydrocortisone free alcohol in a variety of inflammatory dermatoses was studied in a group of 300 patients. The hydrocortisone was applied in the form of an ointment or lotion in petrolatum, petrolatum-lanolin, carbowax and vanishing cream bases. The majority of the cases were treated with the hydrocortisone free alcohol in a concentration of 1 and 2½ per cent in a vanishing cream base. The ointment was applied four times daily and, wherever possible, the patients having symmetrical lesions were selected for paired comparison studies.

The authors found that the hydrocortisone acetate and the free alcohol were about equally effective in the variety of conditions treated. Lesions on thin-skinned areas of the body responded better than those on the thicker-skinned areas, probably because of greater absorption of the drug. Treatment with a vanishing cream base appeared to be more effective than with the other bases. In some cases, the 2½ per cent concentration provided greater relief than the 1 per cent concentration. However, in many other cases the 1 per cent concentration gave marked relief within 24 to 48 hours after use. In many cases, the disease relapsed after discontinuation of therapy. In others, however, relapse did not occur. In these cases it was postulated that the drug had a curative effect or else suppressed the disease long enough for natural bodily defenses to effect a cure. Where relapses did occur after discontinuation of treatment, continued treatment with a lower concentration or less frequent application was effective in controlling the condition.

Good response was obtained in the treatment of contact dermatitis, eczematous dermatitis, atopic dermatitis, seborrheic dermatitis, psoriasis, lichen planus, and pruritus ani, vulvae and scroti. There was a striking initial improvement in patients with cutaneous infections with *Candida albicans* which could be continued with monilicidal agents. Only one untoward reaction occurred in this series of patients.

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**The Treatment of Epilepsy With Methylpentynol.** Kennedy, D. G., and Trounce, J. R. *Science* 122:515 (1955). Methylpentynol was investigated for its effects on patients with epilepsy and for its effects on liver function tests. A previous report had suggested that the drug might be useful in the control of epilepsy and had suggested that it might be toxic to the liver.

Six children between the ages of 11 and 16 years and 18 adult male patients were given up to as much as 1.0 Gm. of methylpentynol orally each day for a period of three months. All but one of the patients had both grand and petit mal, the remaining one had psychomotor epilepsy only. Only one patient, a sixteen-year-old boy, showed control of epileptic seizures by the drug. In this one patient,

an additional nine months of outpatient treatment with methylpentynol has resulted in no epileptic seizures.

Liver function tests were performed on all of the children and on 10 of the adults over the three month period. No abnormalities were found. Two of the children became sleepy and depressed during therapy. This cleared rapidly when therapy was discontinued.

The authors concluded that methylpentynol is unlikely to be useful in controlling epileptic seizures. However, it is not apparently toxic in its effects upon the liver.

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#### **Postoperative Vomiting Controlled by Dimenhydrinate.**

Moore, D. C., Bridenbaugh, L. D., Green, J. C., Piccioni, V. F., Adams, P. A., and Lindstrom, C. A. *J. A. M. A.* 159:1342 (1955). Dimenhydrinate was administered intramuscularly on a routine of 50 mg. on call to surgery, 50 mg. upon return from surgery, and 50 mg. every four hours for four doses to an unselected series of 8,849 surgical cases. The incidence of postoperative vomiting among these patients was 13.0 per cent. Among 1,502 surgical patients who did not receive dimenhydrinate, 22.6 per cent experienced vomiting postoperatively.

To try to further rule out the possibility of prejudice, a "double-blind" series of tests were conducted on 394 patients, 195 of whom did receive dimenhydrinate. However, neither the anesthesia department, the floor nurses, nor the attending surgeons knew whether or not these patients were receiving dimenhydrinate. Among those receiving the drug in the double-blind group, 13.3 per cent vomited while 24.1 per cent vomited among those who did not receive the drug.

The authors concluded, therefore, that dimenhydrinate effectively reduces vomiting by about 50 per cent among unselected postoperative patients in the dosage employed. No side reactions other than an occasional case of drowsiness was observed. The usual premedication dose of morphine, scopolamine, or a barbiturate was not varied during this study.

## BOOK NOTICES AND REVIEWS

**Resonance in Organic Chemistry.** By George Willard Wheland. John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y. 1955. vii + 846 pp. Price \$15.00.

This latest text on resonance by Wheland is a very sincere effort to discuss organic chemistry from the resonance viewpoint. The author endeavors to clear up many misleading impressions that have developed in past explanations of the resonance theory by using very precise and detailed discussions. One of the important features of this book is a chapter on the elementary approach to the quantum mechanics necessary to explain the resonance theory. The average reader will find this chapter requires much study and concentration, but with an elementary calculus background he should learn much about the necessary mathematics of the resonance concepts. There is also a table on bond lengths and bond angles in organic molecules and a complete list of references for this table. The nine chapters of which the book consists deal with the resonance theory and its approach to valence, resonance energy, dipole moments, molecular spectra, steric effects, chemical equilibria and chemical reactions as well as the excellent section on the mathematical aspects of the resonance theory. Included of course are a subject and an author index. This is indeed a book designed especially for the chemist who wants to keep abreast of recent developments of the resonance theory.

A. R. GENNARO

**Microbiology—An Introduction.** By Ernest Gray. Philosophical Library, 15 East 40th Street, New York, N. Y., 1955. 175 pages. 5 x 7 $\frac{1}{4}$  x  $\frac{1}{2}$ .

This little book was designed as a simple introduction to Microbiology. It stresses the ecology of microorganisms and the historical background of microbiology. Much general information is presented in a small number of pages. The book includes a Preface, eleven chapters on Microbiology, References, an Index, and twenty-five excellent illustrations.

It provides a much needed approach for a background in Microbiology by linking together the various fields in the biological sciences.

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